ELSEVIER
CrossMark
Urologic Oncology: Seminars and Original Investigations 33 (2015) 65.e9–65.e17
UROLOGIC ONCOLOGY

Original article

The effect of smoking and timing of smoking cessation on clinical outcome in non–muscle-invasive bladder cancer

Anne J. Grotenhuis, M.Sc.[a], Cornelis W. Ebben, M.Sc.[b], Katja K. Aben, Ph.D.[a,b], J. Alfred Witjes, M.D., Ph.D.[c], Alina Vrieling, Ph.D.[a], Sita H. Vermeulen, Ph.D.[a,d], Lambertus A. Kiemeney, Ph.D.[a,c,*]

[a] *Department for Health Evidence, Radboud university medical center, Nijmegen, The Netherlands*
[b] *Comprehensive Cancer Center the Netherlands, Utrecht, The Netherlands*
[c] *Department for Urology, Radboud university medical center, Nijmegen, The Netherlands*
[d] *Department of Human Genetics, Radboud university medical center, Nijmegen, The Netherlands*

Received 5 February 2014; received in revised form 30 April 2014; accepted 5 June 2014

Abstract

Objectives: Cigarette smoking is the most important risk factor for urinary bladder cancer. The prognostic effect of cigarette smoking on disease recurrence and progression in patients with non–muscle-invasive bladder cancer (NMIBC), however, is still unclear. We evaluated the effect of smoking status and intensity, and timing of smoking cessation, on NMIBC prognosis.

Methods and materials: A population-based series of patients diagnosed with NMIBC from 1995 until 2010 was identified through the Netherlands Cancer Registry. Self-reported smoking history was obtained by a postal lifestyle questionnaire at study inclusion. Detailed clinical data concerning diagnosis, treatment, and disease course were collected retrospectively through a medical file survey. The association of smoking variables with recurrence- and progression-free survival of 963 patients with primary NMIBC was studied using cumulative incidence curves and competing risk regression analyses.

Results: The study population comprised 181 never smokers (18.8%), 490 former smokers (50.9%), and 292 current smokers (30.3%) at the time of diagnosis. No statistically significant difference or trend in risk of recurrence ($P_{trend} = 0.47$) or progression ($P_{trend} = 0.23$) across the 3 smoking status categories was found. Moreover, no dose-response association was observed across categories of smoking quantity, duration, or cumulative exposure in relation to NMIBC prognosis. The timing of smoking cessation (i.e., ceased smoking ≥ 10 y before diagnosis, <10 y before diagnosis, vs. current smoker at diagnosis) did not significantly affect the risk of recurrence ($P_{trend} = 0.31$) and progression ($P_{trend} = 0.19$).

Conclusions: Based on our study, smoking status, smoking intensity, or cessation at any time before diagnosis does not seem to alter the risks of recurrence and progression among patients with NMIBC. Patients' smoking history is not useful for the guidance of clinical management decisions. Patients should nevertheless be advised to quit considering the known beneficial effects on other non-NMIBC–related end points such as cardiovascular disease and second primary cancers.

Keywords: Cigarette smoking; Cessation; Non–muscle-invasive bladder cancer; Prognosis; Recurrence; Progression

1. Introduction

The relapsing nature of non–muscle-invasive bladder cancer (NMIBC) requires frequent follow-up visits and repeated treatment [1,2]. Therewith, NMIBC poses an enormous burden on patients and health care systems. Smoking is the most important risk factor for urinary bladder cancer (UBC), with 50% of all UBC attributable to it [3]. Smoking cessation results in a decrease in the risk of primary UBC of 30% after 1 to 4 years and 60% to 70% after 25 or more years [4,5].

Although not extensively investigated, lifestyle may also affect disease prognosis, and it could therefore represent exposures to be avoided or stimulated after the diagnosis is made. Many substances in cigarette smoke are associated

* Corresponding author. Tel.: +31-24-361-3745; fax: +31-24-361-3505.
E-mail address: Bart.Kiemeney@radboudumc.nl (L.A. Kiemeney).

http://dx.doi.org/10.1016/j.urolonc.2014.06.002
1078-1439/

with carcinogenesis of the bladder wall [6]. In addition to a role as initiators of urothelial carcinogenesis, tobacco constituents could exert (direct) tumor-promoting effects through mechanisms such as immunomodulation [7,8]. Through this, past smoking exposure could affect the clinical features and consequently the malignant potential of bladder tumors at the first clinical presentation [9]. Termination of tobacco exposure might favorably alter the disease course of patients.

Despite the increasing number of studies investigating the prognostic effect of tobacco smoking among patients with UBC, no firm conclusions can be drawn yet [10]. Evidence for prognostic implications of (past or continued) cigarette smoking exposure would emphasize the importance of urologists in stimulating patient awareness and smoking cessation. Besides, it could highlight the relevance of ascertainment of patients' smoking history for clinical management decisions. We investigated the prognostic effect of smoking status, smoking intensity, and timing of cessation on the risk of recurrence and progression among a large Dutch population-based series of patients with NMIBC.

2. Materials and methods

2.1. Patient population

This study used data of the Nijmegen Bladder Cancer Study (NBCS) [11]. Patients with UBC diagnosed in 1 of 7 hospitals in the mideastern part of the country were identified through the population-based Netherlands Cancer Registry (NCR) held by the Comprehensive Cancer Center the Netherlands. Patients younger than 75 years at the time of diagnosis were invited to the NBCS by Comprehensive Cancer Center the Netherlands on behalf of the patients' treating physicians. The NBCS started in May 2007 with invitation of patients diagnosed with UBC from 1995 to 2006 who were still alive. Later, the NBCS was expanded with 3 more recently diagnosed patient cohorts (2006–2008, 2008–2009, and 2009–2010) in 3 phases (January 2009, November 2010, and February 2012, respectively). Of all the invitees, 66% agreed to participate. All participants gave written informed consent, and the study was approved by the institutional review board of the Radboud university medical center (Nijmegen, the Netherlands).

For the current analysis, we included patients with NMIBC (stages Ta, T1, and carcinoma in situ [CIS]) at the first diagnosis, with a maximum time from diagnosis until recruitment of 5 years. Reason for using this time window was to minimize chance of bias owing to prevalent sampling or problems with recall of smoking history. We excluded patients with a previous or synchronous (i.e., within 3 mo) diagnosis of upper urinary tract cancer based on NCR information. Vital status of patients at December 31, 2012 was obtained through record linkage of NCR data with the Dutch Municipal Personal Records Database. Detailed clinical data concerning diagnosis, treatment, and disease course were collected retrospectively through a medical file survey.

2.2. Smoking assessment

At study inclusion, self-reported smoking history of participants was determined by a postal lifestyle questionnaire. Data were collected concerning smoking status (never, former, and current) at recruitment; age at smoking initiation and cessation; the (average) number of cigarettes, cigars, and pipe smoked per day; and number of years of smoking cigarettes, cigars, and pipe. In case of intermittent periods of smoking cessation, patients were asked to sum the years of the periods they smoked.

In this study, "*never smokers*" (NS) were defined as patients who reported to have never smoked cigarettes. Among ever cigarette smokers, smoking status at diagnosis was determined. For this, timing of smoking cessation was calculated as the difference between the age at diagnosis (i.e., age at the initial transurethral resection of the tumor [TURT]) and reported age at cessation. The category of "*current smokers (CS)*" comprised individuals who still smoked in the year of their diagnosis. This group was further stratified in 2 groups: those who quitted smoking within 1 year after their diagnosis ("quitters") and those who did not ("continuing smokers"). Among patients who quitted smoking before diagnosis (i.e., "*former smokers (FS)*"), 2 strata were defined based on the time elapsed since smoking cessation (<10 or ≥ 10 y). All analyses were repeated after excluding 61 and 146 cigar and pipe smokers from the never and ever cigarette smokers category, respectively.

In continuing smokers, only the smoking years before diagnosis were considered. Cumulative smoking exposure was expressed in pack-years, calculated by multiplying cigarette smoking duration in years and number of cigarettes per day divided by 20.

2.3. Verification of smoking status categorization

A telephone survey was performed to verify timing of smoking cessation with respect to diagnosis. For this survey, we selected a subset of patients who reported an age at cessation within 2 years before or after their age at diagnosis. In total, 46 of the 96 patients matching these criteria and still alive were contacted. Results of this survey are summarized in Table S1. In general, our smoking status categorization was judged to be valid based on this survey. However, the survey highlighted the difficulty in accurately distinguishing patients who quitted shortly before or after diagnosis, and quitters from continuing smokers.

2.4. Outcome definition and statistical analyses

Patient and tumor characteristics were compared among the 3 smoking categories using chi-square, Fisher exact, and one-way analysis of variance tests where appropriate.

The prognostic end points were recurrence- and progression-free survival (RFS and PFS). *Recurrence* was defined as a new, histologically confirmed bladder or prostatic urethra tumor following at least 1 tumor-negative follow-up cystoscopy result or 2 surgical resection sessions for the primary tumor. *Progression* was defined as the first occurrence of grade progression, stage progression, local or distant metastasis, and cystectomy for therapy-resistant ("uncontrollable") disease. In addition, we used a stricter progression definition, i.e., transition to muscle-invasive bladder cancer (MIBC; ≥T2). Patients with NMIBC who had an immediate radical cystectomy after primary diagnosis ($n = 21$) were considered not at risk of (intravesical) disease recurrence and progression to MIBC and were therefore excluded.

To evaluate the association between smoking and NMIBC recurrence and progression, competing risk analyses were conducted, as smoking is associated with several health problems that increase mortality. RFS and PFS were defined as the time period between date of the initial TURT and date of the first event (recurrence or progression, respectively), date of the last urological checkup, date of death (during urological follow-up), or date of 5-year follow-up, whichever came first. Death was treated as a competing event. For progression to MIBC, radical cystectomy (without a prior or simultaneous event) was also treated as competing event.

Cumulative incidence curves were constructed and compared among the 3 smoking strata using Gray's test [12]. Univariable and multivariable competing risk regression analyses were used to calculate subdistribution hazard ratios and 95% CIs for smoking variables in relation to prognosis [13]. In a first multivariable model, smoking status (never/ever and never/former/current) was included in conjunction with the prognostic factors tumor stage, grade, and focality; concomitant CIS; and initial treatment. A second multivariable analysis was performed to simultaneously evaluate the prognostic relevance of (cigarette) smoking intensity and timing of smoking cessation among the subset of ever smokers, again in conjunction with aforementioned prognostic factors. Smoking intensity was entered once as the combination of cigarette smoking quantity and duration, and alternatively as the combined cumulative exposure measure. All univariable and multivariable models were fitted by entering smoking variables as categorical variables. A possible dose-response relationship was evaluated by entering smoking variables as ordinal variables, and statistical significance was tested using the Wald test. A two-sided $P < 0.05$ was considered statistically significant.

Missing treatment values were imputed with the most frequent treatment category in the data set for each corresponding combination of tumor stage, grade, and concomitant CIS. Multiple imputation of missing values for tumor focality was conducted using SPSS v20.0 (IBM Corp., Armonk, NY) based on the joint distribution of tumor stage, grade, concomitant CIS, treatment, recurrence status, and tumor focality. For each missing value, 5 imputations were generated. Model estimates of multivariable regression analyses were pooled across the 5 resulting data sets.

Statistical analyses were performed using R v3.0.1 with packages cmprsk and mitools.

3. Results

3.1. Patient characteristics

The study population consisted of 963 patients with newly diagnosed NMIBC. Median time from the initial TURT until date of the last urological checkup was 3.7 years (interquartile range: 2.7–4.7). Distribution of the timing of smoking assessment with respect to NMIBC diagnosis was as follows: 76 (7.9%) within 1 year, 379 (39.4%) between 1 and 2 years, 299 (31.0%) between 2 and 3 years, 115 (11.9%) between 3 and 4 years, and 94 (9.8%) between 4 and 5 years. The numbers in the 3 smoking status strata were as follows: NS: 181 (18.8%), FS: 490 (50.9%), and CS: 292 (30.3%). Among CS, 75 patients were quitters and 217 were continuing smokers.

Descriptive characteristics by smoking status are shown in Table 1. Notable differences between the strata are the lower mean age in CS and the difference in the distribution of sex. As expected, smoking duration and cumulative exposure were higher among CS than FS. FS had a significantly higher and CS a lower proportion of high-grade tumors compared with NS. The proportion of patients who received adjuvant intravesical treatment was lower among CS compared with NS and FS. All other variables were comparable among the 3 strata.

3.2. Association of smoking status with NMIBC prognosis

During the first 5 years after diagnosis, 368 patients with NMIBC (cumulative incidence: 45.1%) had ≥1 recurrence. The 5-year cumulative incidence of NMIBC progression was 17.2% ($n = 129$ events). In 41 patients, this concerned progression to MIBC, which corresponds to a 5-year cumulative risk of 5.5%. Based on univariable analysis, an increased risk of all 3 prognostic end points was observed among ever smokers compared with NS, though nonsignificant ($P = 0.53$ for recurrence, and $P = 0.55$ and 0.30 for broad and stricter definition of progression, respectively) (Table 2). Categorization of the smokers group revealed a tendency toward lower RFS and (in particular) PFS among FS compared with NS/CS (Gray's $P = 0.18$ for recurrence, and $P = 0.03$ for both progression types; Fig.). There was no significant trend in RFS and PFS across the 3 smoking status categories (Table 2).

Also after adjustment for clinicopathological characteristics and treatment, no significant trend in clinical outcome across the smoking categories was observed (Table 2). Owing to the high number of missing values, we were

Table 1
Descriptive characteristics of 963 included patients with primary non–muscle-invasive bladder cancer (NMIBC) according to smoking status at diagnosis

n (%)	Smoking status at diagnosis			*P* value[a]
	Never (*n* = 181)	Former (*n* = 490)	Current (*n* = 292)	
Sex				
Male	125 (69.1)	433 (88.4)	233 (79.8)	**$<1 \times 10^{-6}$**
Female	56 (30.9)	57 (11.6)	59 (20.2)	
Age at diagnosis, y				
Mean ± SD (range)	63 ± 11 (29–92)	66 ± 7.8 (32–91)	61 ± 9.1 (25–81)	**$<1 \times 10^{-6}$**
Smoking quantity (no. of cig./d)				
Mean ± SD (range)	N/A	15.6 ± 9.5 (1–70)	15.2 ± 6.0 (1–40)	0.53
Unknown	N/A	3	–	
Smoking duration, y[b]				
Mean ± SD (range)	N/A	26.9 ± 12.9 (1–57)	39.0 ± 12.8 (1–66)	**$<1 \times 10^{-6}$**
Unknown	N/A	27	18	
Cum. smoking exposure (PYs)[b]				
Mean ± SD (range)	N/A	22.4 ± 17.9 (0.1–120)	30.2 ± 15.5 (0.1–98)	**$<1 \times 10^{-6}$**
Unknown	N/A	30	18	
Tumor stage				
Ta	128 (72.3)	326 (67.4)	210 (73.2)	0.24
T1	41 (23.2)	142 (29.3)	65 (22.6)	
CIS	8 (4.5)	16 (3.3)	12 (4.2)	
Unknown	4	6	5	
Concomitant CIS				
No	165 (92.7)	448 (92.2)	267 (92.7)	0.96
Yes	13 (7.3)	38 (7.8)	21 (7.3)	
Unknown	3	4	4	
Tumor grade[c]				
Low	116 (64.4)	278 (57.2)	194 (67.8)	**0.01**
High	64 (35.6)	208 (42.8)	92 (32.2)	
Unknown	1	4	6	
Tumor focality[d]				
Solitary	97 (57.7)	263 (55.8)	169 (59.9)	0.55
	104 (57.5)	272 (55.5)	174 (59.6)	
Multiple	71 (42.3)	208 (44.2)	113 (40.1)	
	77 (42.5)	218 (44.5)	118 (40.4)	
Unknown	13	19	10	
	–	–	–	
Tumor size				
<3 cm	24 (55.8)	64 (59.3)	46 (65.7)	0.53
≥3 cm	19 (44.2)	44 (40.7)	24 (34.3)	
Unknown	138	382	222	
Initial treatment[e]				
TURT only (±1 p.o. i.v. CT instillation)	79 (43.9)	211 (43.5)	154 (52.7)	**0.04**
	79 (43.6)	212 (43.3)	154 (52.7)	
Adjuvant i.v. CT	62 (34.4)	162 (33.4)	78 (26.7)	
	63 (34.8)	164 (33.5)	78 (26.7)	
Adjuvant i.v. IT	38 (21.1)	107 (22.1)	52 (17.8)	
	38 (21.0)	109 (22.2)	52 (17.8)	
Both adjuvant i.v. CT and IT	1 (0.6)	4 (0.8)	8 (2.7)	
	1 (0.6)	4 (0.8)	8 (2.7)	
Other	–	1 (0.2)	–	
	–	1 (0.2)	–	
Unknown	1	5	–	
	–	–	–	

Note: Values in boldface type indicate significance at $P < 0.05$.
cig. = cigarettes; CT = chemotherapy; Cum. = cumulative; IT = immunotherapy; i.v. = intravesical; N/A = not applicable; p.o. = postoperative; PYs = pack-years; SD = standard deviation.

[a] *P* value is based on chi-square, Fisher exact, or one-way ANOVA test, where appropriate. Missing data were not included in the calculation of *P* values.

[b] Corrected for smoking years after diagnosis in current smokers.

[c] Low grade: WHO 1973 differentiation grade 1 or 2, WHO/ISUP 2004 low grade, or Malmström (Modified Bergkvist) grade 1 or 2a; high grade: WHO 1973 differentiation grade 3, WHO/ISUP 2004 high grade, or Malmström (Modified Bergkvist) grade 2b or 3.

[d] The first line gives the numbers and percentages in the original data set. The second line gives the pooled numbers and percentages based on the 5 imputed data sets (in each data set, 42 missing values for tumor focality are imputed).

[e] The first line gives the numbers and percentages in the original data set. The second line gives the numbers and percentages after single imputation of 6 missing values for treatment.

Table 2
Univariable and multivariable analyses of smoking status in relation to risk of recurrence and progression among 963 patients with primary non–muscle-invasive bladder cancer (NMIBC)

Prognostic end point	Smoking status	Univariable analysis				Multivariable analysis[a]			
		n	*n* Events[b]	Crude sHR (95% CI)	*P* value[c]	*n*	*n* Events[b]	Adj. sHR (95% CI)	*P* value[c]
Disease recurrence	Never	181	63	1.00 (ref)	0.53	177	61	1.00 (ref)	0.68
	Ever	782	305	1.09 (0.83–1.43)		765	298	1.06 (0.80–1.41)	
	Never	181	63	1.00 (ref)	0.52	177	61	1.00 (ref)	0.47
	Former	490	202	1.18 (0.89–1.57)		482	199	1.14 (0.85–1.53)	
	Current	292	103	0.95 (0.70–1.31)		283	99	0.93 (0.67–1.29)	
Disease progression[d]	Never	181	21	1.00 (ref)	0.55	177	20	1.00 (ref)	0.57
	Ever	782	108	1.15 (0.72–1.83)		765	104	1.15 (0.72–1.84)	
	Never	181	21	1.00 (ref)	0.19	177	20	1.00 (ref)	0.23
	Former	490	79	1.38 (0.85–2.22)		482	76	1.36 (0.84–2.21)	
	Current	292	29	0.80 (0.46–1.39)		283	28	0.80 (0.45–1.42)	
Disease progression[e]	Never	181	5	1.00 (ref)	0.30	177	4	1.00 (ref)	0.25
	Ever	782	36	1.64 (0.64–4.18)		765	34	1.85 (0.65–5.28)	
	Never	181	5	1.00 (ref)	0.37	177	4	1.00 (ref)	0.54
	Former	490	29	2.14 (0.83–5.51)		482	28	2.33 (0.82–6.65)	
	Current	292	7	0.84 (0.26–2.65)		283	6	0.92 (0.25–3.35)	

Note: Owing to missing data for covariables, adjusted hazard ratios are based on a smaller number of patients.
Adj. = adjusted; CI = confidence interval; ref = reference group; sHR = subdistribution hazard ratio.
[a]Effect estimates are adjusted for the prognostic factors such as tumor stage (Ta/T1/CIS), tumor grade (high vs. low), concomitant CIS (yes vs. no), tumor focality (multiple vs. solitary), and initial treatment (TURT only/adjuvant intravesical [i.v.] chemotherapy/adjuvant i.v. immunotherapy/both adjuvant i.v. chemotherapy and immunotherapy). Effect estimates were pooled across the 5 data sets with imputations for missing values of tumor focality and treatment.
[b]Number of events within 5 years after the first non–muscle-invasive bladder cancer diagnosis.
[c]*P* value is based on Wald test derived from the univariable/multivariable model with smoking status included as ordinal variable.
[d]Broad progression definition (i.e., first occurrence of grade progression, stage progression, occurrence of local metastasis or distant metastasis or both, and cystectomy for therapy-resistant [“uncontrollable”] disease).
[e]Stricter progression definition (i.e., transition from NMIBC [Ta, T1, CIS] to MIBC [≥T2]).

unable to adjust for tumor size. Results were not significantly different after exclusion of cigar and pipe smokers (data not shown).

3.3. Association of smoking intensity and timing of cessation with NMIBC prognosis

We simultaneously evaluated the prognostic relevance of smoking intensity and timing of cessation with adjustment for tumor characteristics and treatment in the 782 ever smokers (Table 3).

Based on the first multivariable model (*Model 1*), no dose-response association was observed across categories of smoking quantity (P_{trend} = 0.62 and 0.95) or smoking duration (P_{trend} = 0.61 and 0.15) in relation to recurrence and progression, respectively. However, some indications were found for a trend toward a lower risk of progression with increasing smoking duration. In a second multivariable model (*Model 2*), we included smoking intensity expressed in pack-years. No significant trend in RFS and PFS was observed across the categories of cumulative exposure (P_{trend} = 0.98 and 0.28, respectively). In both models, the 2 categories of FS were found to have (a nearly significant) higher risk of recurrence and progression than CS. Although the increase in risk was less pronounced among patients who quitted smoking ≥10 years before diagnosis, longer time since smoking cessation did not seem to beneficially affect disease prognosis (Table 3).

In a secondary analysis, we reran the multivariable analyses with CS split into quitters and continuing smokers (Table S2). This resulted in a negligible change in point estimates and significance level for the smoking intensity measures. The increased risk of recurrence and progression among both FS groups became more pronounced compared with continuing smokers. Although numbers were too small for a robust estimate, quitters were found to have a nonsignificant increased risk of both end points compared with continuing smokers in both models.

The small event number (n = 36) among ever smokers did not allow proper evaluation of these smoking variables in relation to the stricter definition of progression (i.e., shift to MIBC).

4. Discussion

We did not find evidence for an association of cigarette smoking exposure with NMIBC prognosis. No consistent trend

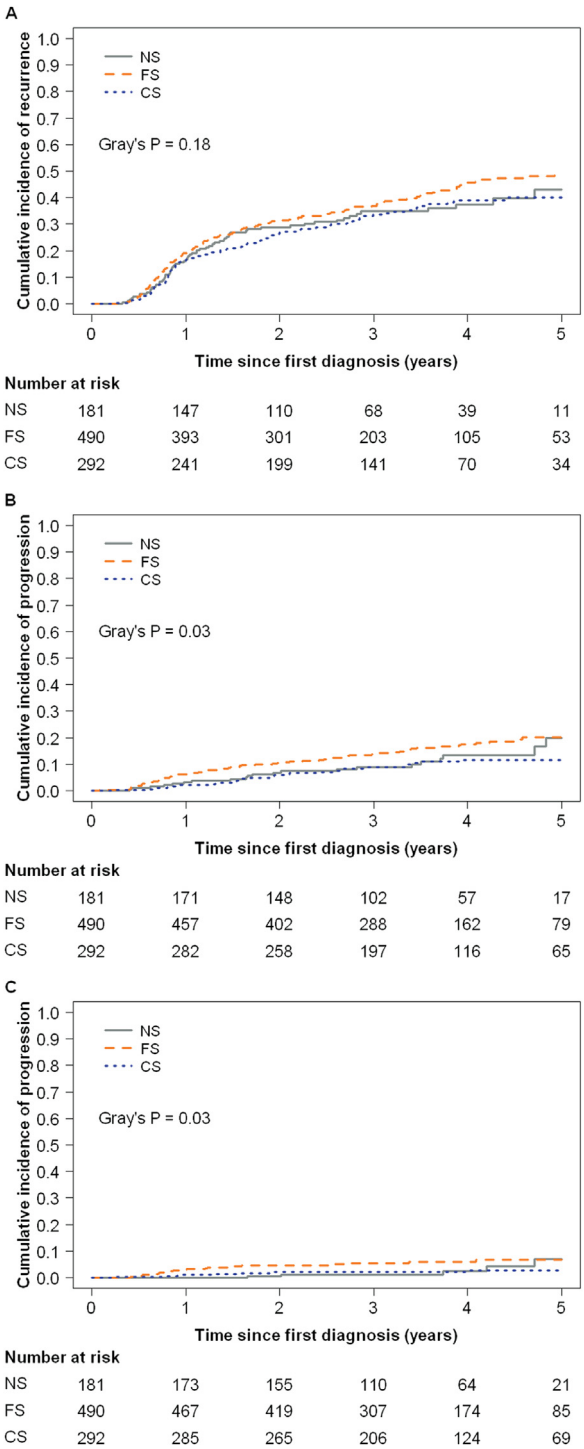

Fig. Cumulative risk of disease recurrence and progression in patients with non–muscle-invasive bladder cancer (NMIBC) by smoking status. Cumulative incidence curves for (A) disease recurrence, (B) disease progression according to broad definition, and (C) disease progression according to stricter definition (i.e., progression to muscle-invasive disease) in non–muscle-invasive bladder cancer (NMIBC) patients by smoking status. The number of individuals at risk at specified time points in each of the smoking groups is indicated below the plots. (Color version of figure is available online.)

in tumor characteristics at the first clinical presentation was observed across the 3 smoking status strata. Neither smoking status at diagnosis nor smoking intensity was significantly associated with risk of recurrence or progression. The hypothesis that (longer time since) smoking cessation improves clinical outcome of patients with NMIBC was rejected.

A recent article by Crivelli et al. [10] describes the current evidence base for prognostic relevance of smoking in patients with urothelial carcinoma. Based on a literature review, 14 studies ($n = 5{,}990$) were identified that evaluated the effect of smoking on clinical outcome among patients with NMIBC. In half of these studies, this was not the primary research aim. Most studies were of relatively small sample size ($n < 400$), except for a study by Sfakianos et al. [14] ($n = 623$), one by Lammers et al. [15] ($n = 718$), and a multi-center study by Rink et al. [16] ($n = 2{,}043$). The review highlights extensive variation in patient and tumor characteristics, treatment, follow-up period, and exposure definition and assessment across studies, which complicates comparison of results. Most reviewed studies indicated that (increasing exposure to) smoking is associated with worse RFS, though there is a larger controversy on the effect on disease progression.

In 2014 edition of the European Association of Urology guidelines, a recommendation was added that all smokers with confirmed NMIBC should be advised to stop smoking because of the reported improvement in outcome following smoking cessation [17]. However, the evidence supporting this statement is rather limited, with conflicting results across studies, as was also described in the review article [10]. Most studies investigated the effect of smoking cessation by comparing recurrence and progression risk between CS and FS at diagnosis, and some did additionally evaluate the effect of varying time elapsed since cessation among FS. Serretta et al. [18] described increased risk of recurrence in both FS and CS compared with NS (which was more pronounced among FS). In a study by Lammers et al. [15], no difference was found in recurrence risk between patients who ceased smoking ≥ 15 vs. < 15 years before diagnosis. By contrast, Rink et al. [16,19] concluded that ≥ 10 years of cessation did abrogate the detrimental effect of smoking on clinical outcome among both patients with primary NMIBC and those with recurrent NMIBC.

Most studies used data concerning smoking status and history that were assessed at diagnosis (sometimes collected retrospectively from the medical charts), i.e., not collected in a longitudinal fashion. Therefore, only few studies could evaluate whether smoking cessation at diagnosis could (still) beneficially alter prognosis compared with continued smoking after diagnosis. Fleshner et al. [20] found increased risk of recurrence among continued smokers compared with both quitters (i.e., quitted between 1 y before and up to 3 mo after diagnosis) and ex-smokers

Table 3
Multivariable analysis of smoking intensity and timing of cessation in relation to risk of recurrence and progression among the subset of ever-smoking patients with primary non–muscle-invasive bladder cancer (NMIBC)

	n	Disease recurrence					Disease progression[a]				
		n Events[b]	Model 1[c]		Model 2[d]		*n* Events[b]	Model 1[c]		Model 2[d]	
			Adj. sHR (95% CI)[e]	*P* value[f]	Adj. sHR (95% CI)[e]	*P* value[f]		Adj. sHR (95% CI)[e]	*P* value[f]	Adj. sHR (95% CI)[e]	*P* value[f]
Smoking quantity (cig./d)											
<10	113	37	1.00 (ref)	0.62	X	X	16	1.00 (ref)	0.95	X	X
10–20	504	207	1.24 (0.86–1.79)		X		69	1.04 (0.58–1.87)		X	
>20	100	41	1.22 (0.76–1.93)		X		16	1.02 (0.48–2.18)		X	
Cigarette smoking duration, y[g]											
<10	54	20	1.00 (ref)	0.61	X	X	8	1.00 (ref)	0.15	X	X
10–19	110	49	1.05 (0.62–1.78)		X		20	0.86 (0.37–1.98)		X	
20–29	151	53	0.83 (0.49–1.43)		X		24	0.83 (0.37–1.87)		X	
30–39	161	61	0.88 (0.50–1.52)		X		21	0.59 (0.25–1.40)		X	
≥40	241	102	1.02 (0.59–1.78)		X		28	0.57 (0.25–1.33)		X	
Cumulative smoking exposure (PYs)[g]											
<20	297	108	X	X	1.00 (ref)	0.98	43	X	X	1.00 (ref)	0.28
20–39	286	131	X		1.29 (0.98–1.70)		46	X		1.08 (0.71–1.65)	
40–59	115	42	X		1.01 (0.70–1.46)		10	X		0.67 (0.34–1.32)	
≥60	19	4	X		0.56 (0.21–1.47)		2	X		0.55 (0.14–2.16)	
Smoking status (including timing of cessation)[h]											
Current	265	95	1.00 (ref)	0.31	1.00 (ref)	0.41	28	1.00 (ref)	0.19	1.00 (ref)	0.08
Former <10 y	106	52	1.38 (0.97–1.95)		1.36 (0.96–1.92)		19	1.68 (0.92–3.07)		1.62 (0.89–2.93)	
Former ≥10 y	346	138	1.22 (0.88–1.68)		1.21 (0.91–1.60)		54	1.40 (0.85–2.30)		1.60 (0.98–2.60)	

Note: Numbers do not add up to the total number of ever smokers ($n = 782$) owing to missing data for 1 or more of the included covariables.

Adj. = adjusted; CI = confidence interval; cig. = cigarettes; PYs = pack-years; ref = reference group; sHR = subdistribution hazard ratio.

[a]Broad progression definition (i.e., first occurrence of grade progression, stage progression, occurrence of local metastasis or distant metastasis or both, and cystectomy for therapy-resistant ["uncontrollable"] disease)

[b]Number of events within 5 years after the first non–muscle-invasive bladder cancer diagnosis.

[c]In Model 1, the following smoking variables are simultaneously included: smoking quantity, smoking duration, and smoking status.

[d]In Model 2, the following smoking variables are simultaneously included: cumulative smoking exposure and smoking status.

[e]Effect estimates are adjusted for the prognostic factors such as tumor stage (Ta/T1/CIS), tumor grade (high vs. low), concomitant CIS (yes vs. no), tumor focality (multiple vs. solitary), and initial treatment (TURT only/adjuvant intravesical [i.v.] chemotherapy/adjuvant i.v. immunotherapy/both adjuvant i.v. chemotherapy and immunotherapy). Effect estimates were pooled across the 5 data sets with imputations for missing values of tumor focality and treatment.

[f]*P* value is based on Wald test derived from the multivariable model with all smoking variables included as ordinal variables.

[g]Corrected for smoking years after diagnosis.

[h]Time elapsed since smoking cessation was calculated as the difference between the age at diagnosis (i.e., age at the initial TURT) and reported age at cessation.

(i.e., quitted between 1 and 10 y before diagnosis). Chen et al. [21] also found worse RFS among continued smokers compared with quitters, but ex- and nonsmokers did experience (tendency toward) increased recurrence risk as well. Sfakianos et al. did not detect a beneficial effect of smoking cessation at diagnosis on outcome among bacillus Calmette-Guérin–treated patients with NMIBC [14].

Strengths of our study are the population-based nature and relatively large sample size of well-phenotyped patients with NMIBC with long follow-up. The fact that patients with UBC were selected for study participation based on their vital status may have led to selection of patients with a relatively favorable prognosis. This could bias study results, probably to a larger extent for progression than for recurrence. Therefore, we restricted our analyses to a subset of study participants who were recruited within 5 years after diagnosis. In this sample, we expect selection is negligible considering the high 5-year survival rates in patients with NMIBC and that 78% of the sample was already enrolled within 3 years of diagnosis.

In addition, restriction of the analyses to the patient sample recruited within 5 years after diagnosis did decrease the chance of bias related to patients' ability to recall their smoking history, especially for the period surrounding diagnosis.

In this study, patients were asked for their age at smoking initiation and cessation, and smoking status and time elapsed since cessation at diagnosis were derived from this. Therefore, the precision of timing of cessation was not sufficient to (further) classify patients who ceased smoking shortly before or after diagnosis, and to completely distinguish quitters from continuing smokers. This was also pointed out by our small validation survey. As most recurrences occur within a short time-span after diagnosis, i.e., within 1 or 2 years, this distinction might be relevant. Driven by the importance of the question for clinicians and patients, we however did perform a secondary analysis to investigate whether smoking cessation at diagnosis (according to our categorization) could beneficially influence prognosis. Future studies should focus on extensive and precise (preferably prospective) determination of exposure to cigarette smoke to more accurately assess the prognostic effect of (duration of) continued smoking after diagnosis.

Lack of association could, in theory, be caused by the limitations of our study as stated previously. However, our study findings may also be explained by the theory of "field cancerization" in the sense that independent and irreversible (pre-)malignant transformation of cells, spread across the entire urothelium, has already occurred [22,23]. Next to diagnosis of multiple synchronous (multifocal) tumors, this explains the occurrence of metachronous tumors and why termination of smoking exposure does not beneficially alter recurrence risk.

This study shows that information on smoking status and history is not useful for improving prediction of disease outcome or guiding clinical decision making in NMIBC. Despite the lack of convincing evidence for a prognostic effect, smoking cessation should still be encouraged by urologists in light of the well-established beneficial influence on risk of several other diseases, such as cardiovascular disease and second primary cancers.

Acknowledgments

The authors thank all the participants in the study for their involvement in this research project and their time and effort to complete the questionnaire. They also thank Ursula Oldenhof for performing the telephone survey.

Appendix A. Supporting Information

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.urolonc.2014.06.002.

References

[1] van Rhijn BW, Burger M, Lotan Y, et al. Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. Eur Urol 2009;56:430–42.
[2] Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013;64:639–53.
[3] Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. J Am Med Assoc 2011;306:737–45.
[4] Brennan P, Bogillot O, Cordier S, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. Int J Cancer 2000;86:289–94.
[5] Brennan P, Bogillot O, Greiser E, et al. The contribution of cigarette smoking to bladder cancer in women (pooled European data). Cancer Causes Control 2001;12:411–7.
[6] Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol 2013;63:234–41.
[7] Gabriel U, Li L, Bolenz C, et al. New insights into the influence of cigarette smoking on urothelial carcinogenesis: smoking-induced gene expression in tumor-free urothelium might discriminate muscle-invasive from nonmuscle-invasive urothelial bladder cancer. Mol Carcinog 2012;51:907–15.
[8] Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol 2002;2:372–7.
[9] van Roekel EH, Cheng KK, James ND, et al. Smoking is associated with lower age, higher grade, higher stage, and larger size of malignant bladder tumors at diagnosis. Int J Cancer 2013;133:446–54.
[10] Crivelli JJ, Xylinas E, Kluth LA, Rieken M, Rink M, Shariat SF. Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. Eur Urol 2013;65:742–54.
[11] Rafnar T, Vermeulen SH, Sulem P, et al. European genome-wide association study identifies SLC14A1 as a new urinary bladder cancer susceptibility gene. Hum Mol Genet 2011;20:4268–81.
[12] Gray RJ. A class of *K*-sample tests for comparing the cumulative incidence of competing risk. Ann Stat 1988;16:1140–54.
[13] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
[14] Sfakianos JP, Shariat SF, Favaretto RL, Rioja J, Herr HW. Impact of smoking on outcomes after intravesical bacillus Calmette-Guerin therapy for urothelial carcinoma not invading muscle of the bladder. BJU Int 2011;108:526–30.
[15] Lammers RJ, Witjes WP, Hendricksen K, Caris CT, Janzing-Pastors MH, Witjes JA. Smoking status is a risk factor for recurrence after transurethral resection of non-muscle-invasive bladder cancer. Eur Urol 2011;60:713–20.

[16] Rink M, Furberg H, Zabor EC, et al. Impact of smoking and smoking cessation on oncologic outcomes in primary non-muscle-invasive bladder cancer. Eur Urol 2013;63:724–32.
[17] Babjuk M, Böhle A, Burger M, et al. Guidelines on non-muscle-invasive bladder cancer (Ta, T1 and CIS). Uroweb. Available at: http://www.uroweb.org/gls/pdf/05%20Non-muscle%20Invasive%20BC_TaT1_LR.pdf; 2014.
[18] Serretta V, Altieri V, Morgia G, et al. Cigarette smoking status at diagnosis and recurrence in intermediate-risk non-muscle-invasive bladder carcinoma. Urology 2013;81:277–81.
[19] Rink M, Xylinas E, Babjuk M, et al. Impact of smoking on outcomes of patients with a history of recurrent nonmuscle invasive bladder cancer. J Urol 2012;188:2120–7.
[20] Fleshner N, Garland J, Moadel A, et al. Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. Cancer 1999;86:2337–45.
[21] Chen CH, Shun CT, Huang KH, et al. Stopping smoking might reduce tumour recurrence in nonmuscle-invasive bladder cancer. BJU Int 2007;100:281–6.
[22] Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res 2003;63:1727–30.
[23] Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6:963–8.